Meat intake, meat cooking methods, and meat-derived mutagen exposure and risk of sessile serrated lesions

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ABSTRACT

Background: Red and processed meat, recognized carcinogens, are risk factors for colorectal neoplasia, including polyps, the precursor for colorectal cancer. The mechanism is unclear. One possible explanation is the mutagenic activity of these foods, perhaps due to generation during cooking [e.g., heterocyclic amine (HCA) intake]. Few studies have evaluated meat intake and sessile serrated lesion (SSL) risk, a recently recognized precursor, and no study has evaluated meat cooking methods and meat-derived mutagens with SSL risk.

Objective: We evaluated intakes of meat, meat cooking methods, and inferred meat mutagens with SSL risk and in comparison to risk of other polyps.

Methods: Meat, well-done meat, and inferred meat mutagen intakes were evaluated. Polytomous logistic regression models were used to estimate ORs and 95% CIs among cases (556 hyperplastic polyp, 1753 adenoma, and 208 SSL) and controls (3804) in the large colonoscopy-based, case-control study, the Tennessee Colorectal Polyp Study.

Results: The highest quartile intakes of red meat (OR: 2.38; 95% CI: 1.44, 3.93), processed meat (OR: 2.03; 95% CI: 1.30, 3.17), well-done red meat (OR: 2.19; 95% CI: 1.34, 3.60), and the HCA 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQX; OR: 2.48; 95% CI: 1.49, 4.16) were associated with increased risk of SSLs in comparison to the lowest quartile intake.

Conclusions: High intakes of red and processed meats are strongly and especially associated with SSL risk and part of the association may be due to HCA intake. Future studies should evaluate other mechanism(s) and the potential for primary prevention. *Am J Clin Nutr* 2020;111:1244–1251.

Keywords: sessile serrated lesion, colorectal, adenoma, meat, heterocyclic amines, polycyclic aromatic hydrocarbons, etiology

Introduction

Colorectal cancer (CRC) is the third most common cancer in the United States and the second leading cause of cancer-related mortality (1). The primary pathway to CRC is the conventional adenoma (AD)–carcinoma sequence (also known as the chromosomal instability pathway) (1, 2). There are other

colorectal polyps in addition to AD. Hyperplastic polyps (HPs) are a common polyp type that has been presumed to be benign with little malignant potential. Within the past 2 decades, a third type of colorectal polyp, the sessile serrated lesion (SSL), has been recognized. A diagnostic consensus for SSL was not reached until 2010 (1, 3–6). SSLs represent an alternative pathway to carcinogenesis, which may account for 20–30% of CRCs (7, 8), particularly microsatellite instable cancer (9).

Recent studies suggest that SSLs are overrepresented in interval cancers, which may represent the potential for more rapid conversion to malignancy or may reflect their difficulty to locate on colonoscopy, which may lead to missed lesions (10). Thus, it is valuable to understand how the development of these polyps might be impacted by modifiable lifestyle factors. However, given the recency of the SSL diagnosis consensus, there are few epidemiologic studies that have evaluated risk factors for SSLs.

The WHO has classified red meat as a class 2A carcinogen, indicating that it probably causes cancer, and processed meat as a group 1 carcinogen, indicating that it is known to cause cancer. A recent expert panel report also supported a role for red and processed meats in CRC risk (11). Meat-derived mutagens may account for red and processed meat carcinogenicity. Heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are generated during high-temperature cooking of meat whose reactive metabolites may cause DNA damage. Their mutagenic activity varies based on many factors including the method of cooking, cooking time, and temperature (12). HCAs become capable of damaging DNA when they are activated by specific enzymes in the body; the bioactivity of these enzymes differs among people and may contribute to cancer risks associated with exposure to HCAs (13, 14). One potential mechanism that could explain the mutagenicity of HCAs and PAHs is the formation of DNA adducts, which increase with the intake of dietary HCAs and PAHs (12, 15).

There are few studies that have evaluated the association of meat intake and inferred meat-derived mutagens with SSLs, including our previous publication evaluating total red meat intake in which we observed a strong association between red meat intake and SSLs (16). However, to our best knowledge, no previous study has evaluated the risk of SSLs with processed meat intake, meat doneness levels, or inferred meat-mutagen intake. In this study, we conduct this analysis and compare risks for SSLs with risks for AD and HP.

Methods

Study design and population

Data from the case-control Tennessee Colorectal Polyp Study (TCPS) was used in this analysis. Details of the study design have been previously published (16). In brief, the TCPS was conducted from February 2003 to October 2010 and included 7621 participants recruited from colonoscopy clinics at Vanderbilt University Medical Center and the Tennessee Valley Veterans Affairs Medical Center (**Supplemental Figure 1**). The primary outcome of the TCPS was risk of colorectal polyps. The study was approved for human subjects research by both institutions, and all study participants provided written informed consent. Individuals were excluded if they had a personal history of adenoma, cancer, inflammatory bowel disease, or familial CRC syndrome.

The majority of participants (90.5%) were recruited prior to colonoscopy before their examination findings were known.

Patient and public involvement

During the multiyear fielding of this study, patient advocates were included in the study team and participated in review of study procedures, progress, and research findings.

Meat and inferred meat-mutagen intake amounts

Of the 7621 participants providing an informed written consent and participating in ≥1 component of the study, 6462 (84.3%) completed an interviewer-administered telephone questionnaire that solicited information about family history, health history, and lifestyle factors, including a detailed assessment of meat intake and meat doneness using an at-home booklet with pictures of cooked meats, which has been previously described in detail (Supplemental Figure 1) (17). Intakes of other dietary factors were collected from a self-administered FFQ developed to capture dietary intake in the southeastern United States (18).

Participants were asked about their usual intake in the past 12 mo of 11 meats (hamburgers or cheeseburgers from fast food, hamburgers or cheeseburgers not from fast food, beef steaks, pork chops or ham steaks, bacon, sausage, hotdogs or franks, chicken, fish, meat gravies made with drippings, and short ribs or spareribs). For each meat, participants were asked to report their usual intake frequency (never or once a month or less, 2–3 times/mo, once a week, 2–3 times/wk, 4–6 times/wk, once a day, or ≥2 times/d) and serving size (small, medium, or large based on specified weights) and the frequency (never, about one-quarter of the time, about one-half of the time, about three-quarters of the time, and always) of ≤5 different cooking methods (oven-broiled or oven-baked, grilled or barbecued, pan-fried, deep fried, or all other ways). In addition, participants were asked to select their preference for meat doneness level for 7 different types of meat or preparations of meat (hamburger, cheeseburger, or beef patties, beef steaks, pork chops, bacon, grilled chicken, pan-fried chicken, and pan-fried or grilled fish) using a series of 3 photographs in their at-home booklet of each meat cooked to increasing doneness levels. Intakes of meat were converted to inferred meat-derived mutagens based on the amount of meat intake and the usual level of meat well-doneness using the software CHARRED created by the National Cancer Institute as previously described (19). This analysis examined the following specific mutagens: 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQX), 2-amino-3,4,8-trimethylimidazo[4,5-f]-quinoxaline (DiMeIQX), 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), benzo[α]pyrene (BaP), and total mutagenic activity.

Case and control definitions

Individuals were classified into polyp cases or controls based on the findings at the colonoscopy. All colonoscopies were performed as part of routine care using standard clinical practice. Individuals were classified as a control if they had no polyps at the colonoscopy during a complete colonoscopy with confirmed visualization of the cecum ($n = 3804$). Individuals with polyps

TABLE 1 Characteristics of the study participants in the Tennessee Colorectal Polyp Study[1]

Characteristics	No-polyp controls (n = 3803)	HPs (n = 559)	ADs (n = 1787)	SSLs (n = 212)	P-heterogeneity[2]	P for SSL vs. other groups[2,3]		
						Controls	HP	AD
Age, y	57.2 (56.9, 57.4)	56.8 (56.2, 57.4)	59.0 (58.6, 59.3)	57.2 (56.7, 58.8)	<0.001	0.307	0.124	0.023
Sex, % F	44.8	36.1	28.0	36.3	<0.001	0.016	0.962	0.012
Race, % white	89.4	91.1	88.9	91.1	0.226	0.071	0.489	0.450
Study site, %					<0.001			
Academic medical center	74.9	66.7	66.8	69.3				
Veterans Affairs medical center	25.1	33.3	33.2	30.7				
Educational attainment, %					<0.001	0.056	0.548	0.555
High school or less	23.3	29.3	28.5	24.4				
Some college	28.4	28.3	28.3	27.3				
College graduate	21.3	21.8	22.1	27.6				
Graduate/professional school	26.9	20.6	21.1	21.1				
Indication for colonoscopy, %					0.172			
Average risk screening	57.1	54.1	55.3	57.5				
Family history	12.6	13.7	12.7	16.3				
Diagnostic/follow-up	22.5	21.6	23.7	15.7				
Other	7.8	10.5	8.3	10.5				
Family history of colorectal cancer, %	9.0	8.7	9.3	12.0	0.006	0.008	0.125	0.217
Regular alcohol intake, %					0.016	0.130	0.958	0.360
Never	59.5	53.5	56.3	53.8				
Former	21.6	23.7	23.9	21.8				
Current	18.8	22.8	19.8	24.4				
Cigarette smoking status, %					<0.001	<0.001	0.276	0.076
Never	53.2	31.7	42.8	37.0				
Former	34.2	38.1	33.3	33.2				
Current	12.6	30.1	23.9	29.8				
Regular physical activity in the past 10 y, %	58.3	53.2	52.3	52.6	<0.001	0.184	0.942	0.700
Current use of NSAIDs, %	51.7	50.9	45.7	44.7	<0.001	0.007	0.066	0.204
BMI, kg/m^2	28.0	28.8	28.7	28.8	<0.001	0.058	0.861	0.852
Total energy intake, kcal/d	2048 (2011, 2086)	2173 (2084, 2261)	2162 (2108, 2215)	2031 (1891, 2172)	<0.001	0.818	0.090	0.082

[1]Values are least-square means of log transformed data (lower confidence limit, upper confidence limit) or frequencies standardized to age (5-y categories) and sex distribution of controls, with the exception of age, sex, race, educational attainment, study site, and indication for colonoscopy which are presented as n (%) for categorical data and least-square means (lower confidence limit, upper confidence limit) for continuous data. Statistical significance was set at $P < 0.0167$. AD, conventional adenoma; HP, hyperplastic polyp; NSAID, nonsteroidal anti-inflammatory drug; SSL, sessile serrated lesion.

[2]P values adjusted for age (5-y categories) and sex for all comparisons excluding age, sex, and study site.

[3]P values for comparisons of SSL cases vs. controls, HP cases, and AD cases where all P-heterogeneity < 0.05.

TABLE 2 Associations between intake of meat types and SSL risk: the Tennessee Colorectal Polyp Study[1]

		SSLs vs. polyp-free controls		SSLs vs. other polyp cases			
			SSL	SSL vs. hyperplastic polyp only		SSL vs. conventional adenoma	
Meat intake amount, g/d (min, max)	Controls, n	n	OR (95% CI)[2]	n	OR (95% CI)[2]	n	OR (95% CI)[2]
Total meat							
Q1: (0, <59.4)	951	35	1.00 (ref)	101	1.00 (ref)	394	1.00 (ref)
Q2: (59.4, <90.9)	951	44	1.43 (0.88, 2.34)	116	1.22 (0.7, 2.12)	339	1.67 (1.01, 2.76)
Q3: (90.9, <138.5)	951	61	1.81 (1.13, 2.90)	158	1.29 (0.76, 2.18)	459	1.76 (1.09, 2.85)
Q4: ≥138.5	950	72	2.20 (1.36, 3.56)	184	1.51 (0.88, 2.59)	595	1.96 (1.20, 3.21)
P-trend			<0.001		0.145		0.011
White meat							
Q1: (0, <24.9)	971	54	1.00 (ref)	142	1.00 (ref)	488	1.00 (ref)
Q2: (24.9, <45.3)	931	63	1.42 (0.95, 2.13)	144	1.30 (0.83, 2.05)	451	1.40 (0.93, 2.12)
Q3: (45.3, <85.0)	1269	62	1.11 (0.74, 1.66)	187	0.98 (0.62, 1.55)	525	1.22 (0.80, 1.85)
Q4: ≥85.0	612	32	1.18 (0.72, 1.92)	82	1.17 (0.67, 2.04)	313	1.07 (0.65, 1.76)
P-trend			0.742		0.923		0.813
Red meat							
Q1: (0, <16.3)	965	33	1.00 (ref)	91	1.00 (ref)	306	1.00 (ref)
Q2: (16.3, <39.5)	937	39	1.14 (0.68, 1.91)	123	0.88 (0.49, 1.56)	397	0.96 (0.56, 1.63)
Q3: (39.5, <75.7)	953	56	1.69 (1.04, 2.74)	147	1.29 (0.74, 2.24)	427	1.45 (0.88, 2.39)
Q4: ≥75.7	948	84	2.38 (1.44, 3.93)	198	1.62 (0.92, 2.85)	657	1.69 (1.01, 2.83)
P-trend			<0.001		0.028		0.012
Processed meat							
Q1: (0)	1070	42	1.00 (ref)	118	1.00 (ref)	377	1.00 (ref)
Q2: (1.0, <8.0)	834	37	1.08 (0.66, 1.75)	116	0.84 (0.49, 1.45)	354	1.00 (0.61, 1.65)
Q3: (8.0, <22.5)	944	49	1.27 (0.81, 2.00)	148	1.04 (0.63, 1.74)	439	1.20 (0.75, 1.91)
Q4: ≥22.5	946	84	2.03 (1.30, 3.17)	176	1.72 (1.04, 2.85)	613	1.74 (1.10, 2.74)
P-trend			0.001		0.018		0.011

[1] max, maximum; min, minimum; NSAID, nonsteroidal anti-inflammatory drug; Q, quartile; ref, reference; SSL, sessile serrated lesion.

[2] ORs and 95% CIs were derived from multinomial logistic regression models adjusted for age, sex, race, study site, educational attainment, indication for colonoscopy, alcohol intake, smoking history, physical activity, BMI, total energy intake, and NSAID use. Statistical significance was set at $P < 0.0167$.

were classified into case groups based on the histopathological diagnosis of all retrieved polyps. Diagnoses of all polyps were standardized by a study pathologist as previously described (16). AD cases had ≥1 tubular, tubulovillous, or villous AD without a synchronous SSL. SSL cases had ≥1 SSL. HP cases had ≥1 HP without any other synchronous polyp.

Statistical analysis

The current analysis is based on a total of 6361 eligible participants (86.0%) who completed the telephone interview meat questionnaire, including 212 SSL cases, 559 HP cases, 1787 AD cases, and 3803 polyp-free controls (Supplemental Figure 1). Characteristics were compared between cases and controls using Mantel-Haenszel chi-square testing for categorical variables and general linear models for continuous variables with adjustment for age (5-y categories) and sex, where appropriate. Quantiles were derived for meat and inferred meat-mutagen intake amounts using the distribution among controls. SSL cases were compared with controls, HP cases, and AD cases. The associations between intake and the risks of HPs, ADs, and SSLs were evaluated using multinomial logistic regression models to estimate ORs and 95% CIs. All models were adjusted for sex (male/female), age (years), recruitment site [academic, Veterans Affairs (VA)], race (white, nonwhite), indication for colonoscopy (screening, family history, diagnostic, other), regular alcohol consumption status (never, former, current), cigarette smoking status (never,

former, current), regular exercise in the past 10 y (no/yes), BMI (kg/m²), educational attainment (high school or less, some college, college graduate, graduate/professional school), current regular use of nonsteroidal anti-inflammatory drugs (NSAIDs; no/yes), and total energy intake (kilocalories per day derived from an FFQ). For individuals who did not provide an FFQ ($n = 916$ including 31 SSL cases), total energy intake was imputed by assigning the group mean within age (5-y categories), sex (male/female), and study site (academic/VA) strata. An α of 0.0167 (0.05/3 comparison groups) was used. All statistical analyses were completed using Statistical Analysis System (SAS Enterprise 7.15; SAS Institute).

Ethics approval

Written informed consent was obtained from all study participants, and the study protocol was approved by the institutional review board at each study site.

Results

Demographic characteristics of each of the 4 groups examined (no-polyp controls, ADs, HPs, and SSLs) are shown in **Table 1**. In comparison to controls, SSL cases were more likely to be male ($P = 0.016$) and have a current or past smoking history ($P < 0.001$), a family history of CRC ($P = 0.008$), and a lower use of NSAIDs ($P = 0.007$). In comparison to AD cases, SSL

TABLE 3 Associations between well-done meat intake and SSL risk; the Tennessee Colorectal Polyp Study[1]

	SSLs vs. polyp-free controls			SSLs vs. other polyp cases			
		SSL		SSL vs. hyperplastic polyp only		SSL vs. conventional adenoma	
Well-done meat intake amount, g/d (min, max)	Controls, n	n	OR (95% CI)[2]	n	OR (95% CI)[2]	n	OR (95% CI)[2]
Total well-done meat							
Q1: (0, <24.90)	952	40	1.00 (ref)	109	1.00 (ref)	342	1.00 (ref)
Q2: (24.90, <49.31)	950	32	0.90 (0.55, 1.49)	99	0.99 (0.56, 1.75)	388	0.82 (0.49, 1.38)
Q3: (49.31, <85.20)	951	67	1.65 (1.06, 2.59)	164	1.26 (0.76, 2.09)	455	1.39 (0.88, 2.21)
Q4: ≥85.20	950	73	1.83 (1.15, 2.89)	187	1.46 (0.87, 2.46)	602	1.43 (0.89, 2.29)
P-trend			0.001		0.093		0.035
Total well-done white meat							
Q1: (0, <4.7)	948	46	1.00 (ref)	143	1.00 (ref)	427	1.00 (ref)
Q2: (4.7, <14.2)	948	70	1.55 (1.03, 2.34)	112	0.94 (0.57, 1.55)	490	1.29 (0.85, 1.96)
Q3: (14.2, <29.8)	972	40	1.04 (0.66, 1.64)	162	1.4 (0.86, 2.27)	422	0.95 (0.59, 1.51)
Q4: ≥29.8	924	55	1.43 (0.92, 2.20)	140	0.59 (0.34, 1.04)	442	1.21 (0.78, 1.89)
P-trend			0.362		0.814		0.732
Total well-done red meat							
Q1: (0, <9.50)	985	33	1.00 (ref)	97	1.00 (ref)	320	1.00 (ref)
Q2: (9.50, <28.35)	940	40	1.24 (0.74, 2.05)	124	0.99 (0.56, 1.75)	393	1.07 (0.64, 1.81)
Q3: (28.35, <58.50)	928	60	1.81 (1.12, 2.94)	150	1.38 (0.8, 2.38)	441	1.52 (0.92, 2.49)
Q4: ≥58.50	950	79	2.19 (1.34, 3.60)	188	1.69 (0.97, 2.96)	633	1.68 (1.01, 2.80)
P-trend			<0.001		0.025		0.018
Total well-done processed meat							
Q1: (0)	1529	67	1.00 (ref)	173	1.00 (ref)	572	1.00 (ref)
Q2: (0.10, <3.90)	451	19	0.75 (0.41, 1.35)	60	0.65 (0.34, 1.25)	197	0.68 (0.37, 1.24)
Q3: (3.90, <13.43)	866	45	1.09 (0.72, 1.63)	141	0.83 (0.53, 1.32)	407	1.02 (0.67, 1.56)
Q4: ≥13.43	948	81	1.58 (1.08, 2.31)	184	1.28 (0.83, 1.98)	607	1.38 (0.93, 2.04)
P-trend			0.019		0.304		0.099

[1]max, maximum; min, minimum; NSAID, nonsteroidal anti-inflammatory drug; Q, quartile; ref, reference; SSL, sessile serrated lesion.

[2]ORs and 95% CIs were derived from multinomial logistic regression models adjusted for age, sex, race, study site, educational attainment, indication for colonoscopy, alcohol intake, smoking history, physical activity, BMI, total energy intake, and NSAID use. Statistical significance was set at $P < 0.0167$.

cases were younger ($P = 0.023$) and more likely to be female ($P = 0.012$).

Evaluation of meat type and SSL risk

Table 2 presents results for the associations of meat intake with the risk of SSLs. A nearly 2-fold increased risk of SSLs in comparison to controls was observed for total meat intake for the highest versus the lowest intake quartile. This association appeared to be particularly strong for and limited to red meat (OR: 2.38; 95% CI: 1.44, 3.93; P-trend < 0.001) and processed meat (OR: 2.03; 95% CI: 1.30, 3.17; P-trend = 0.001), with no association observed for intake of total white meat. SSLs were also associated with red meat intake in comparison to ADs (P-trend = 0.012) and suggestively associated with risk in comparison to HPs (P-trend = 0.028), both of which polyp types were also associated with red meat intake in comparison to controls (data not shown). The association with processed meat was only observed for SSLs and not for the other polyp cases versus controls (data not shown).

Evaluation of well-done meat intake and SSL risk

Table 3 presents results for the associations of well-done meat intake with the risk of SSLs. In comparison to controls, an 80% increased risk of SSLs was observed for total well-done meat intake (OR: 1.83; 95% CI: 1.15, 2.89; P-trend = 0.001) as

well as a suggestive 60% increased risk for well-done processed meat (OR: 1.58; 95% CI: 1.08, 2.31; P-trend = 0.019) and a more than double increased risk for well-done red meat intake (OR: 2.19; 95% CI: 1.34, 3.60; P-trend < 0.001) for the highest versus the lowest intake quartile. Well-done red meat intake was also suggestively but not significantly associated with SSLs in comparison to HPs or ADs.

Evaluation of associations between meat mutagens and polyp risk

The associations of specific inferred meat mutagens with the risk of SSLs are presented in Table 4. An increased risk of SSLs was observed for MeIQX intake. Specifically, MeIQX was associated with a strong 2.5-fold increased risk of SSLs in comparison to controls (OR: 2.48; 95% CI: 1.49, 4.16; P-trend = 0.004) and a ≥2-fold increased risk in comparison to HP or AD cases, although the latter findings were not statistically significant. There were no associations observed for intakes of PhIP, DiMeIQX, or BaP and SSL risk.

Discussion

In this large case-control study, higher intakes of total meat, red meat, processed meat, well-done meat, well-done red meat, and well-done processed meat were associated with an increased risk of SSLs. For nearly all meat intake categories associated with

TABLE 4 Associations between intake of inferred meat-derived mutagens and SSL risk: the Tennessee Colorectal Polyp Study[1]

	SSLs vs. polyp-free controls			SSLs vs. other polyp cases			
		SSL		SSL vs. hyperplastic polyp only		SSL vs. conventional adenoma	
Inferred daily intake amount, ng/d (min, max)	Controls, n	n	OR (95% CI)[2]	n	OR (95% CI)[2]	n	OR (95% CI)[2]
MeIQX intake							
Q1: (0, <12.2)	930	27	1.00 (ref)	103	1.00 (ref)	313	1.00 (ref)
Q2: (12.2, <32.9)	930	59	2.17 (1.32, 3.58)	119	2.06 (1.17, 3.60)	379	1.98 (1.18, 3.31)
Q3: (32.9, <70.3)	930	46	1.69 (1.00, 2.84)	155	1.40 (0.79, 2.49)	452	1.41 (0.83, 2.40)
Q4: ≥70.3	929	77	2.48 (1.49, 4.16)	173	2.22 (1.25, 3.93)	597	1.97 (1.16, 3.33)
P-trend			0.004		0.044		0.075
PhIP intake							
Q1: (0, <73.25)	930	40	1.00 (ref)	112	1.00 (ref)	356	1.00 (ref)
Q2: (73.25, <169.38)	930	56	1.30 (0.83, 2.02)	116	1.38 (0.83, 2.30)	385	1.27 (0.81, 2.01)
Q3: (169.38, <336.20)	930	55	1.34 (0.86, 2.09)	152	1.19 (0.72, 1.96)	480	1.08 (0.69, 1.70)
Q4: ≥336.20	929	58	1.39 (0.89, 2.18)	170	1.17 (0.71, 1.93)	520	1.12 (0.71, 1.78)
P-trend			0.173		0.793		0.870
DiMeIQX intake							
Q1: (0, <0.83)	931	45	1.00 (ref)	112	1.00 (ref)	364	1.00 (ref)
Q2: (0.83, <2.74)	930	47	0.98 (0.63, 1.53)	122	1.01 (0.61, 1.67)	394	0.97 (0.61, 1.53)
Q3: (2.74, <5.96)	929	47	0.96 (0.62, 1.50)	142	0.90 (0.54, 1.48)	421	0.93 (0.59, 1.47)
Q4: ≥5.96	929	70	1.38 (0.91, 2.10)	174	1.18 (0.73, 1.91)	562	1.12 (0.73, 1.72)
P-trend			0.131		0.538		0.608
BaP intake							
Q1: (0, <9.10)	930	45	1.00 (ref)	109	1.00 (ref)	343	1.00 (ref)
Q2: (9.10, <31.54)	930	54	1.23 (0.79, 1.90)	133	1.2 (0.73, 1.98)	420	1.12 (0.72, 1.77)
Q3: (31.54, <79.05)	930	50	1.05 (0.66, 1.65)	136	1.02 (0.61, 1.7)	466	0.87 (0.55, 1.39)
Q4: ≥79.05	929	60	1.30 (0.83, 2.03)	172	1.14 (0.69, 1.88)	512	1.09 (0.69, 1.73)
P-trend			0.382		0.820		0.972
Meat-mutagen intake							
Q1: (0, <3645)	930	39	1.00 (ref)	98	1.00 (ref)	333	1.00 (ref)
Q2: (3645, <7234)	930	51	1.36 (0.86, 2.14)	140	1.03 (0.62, 1.73)	403	1.18 (0.74, 1.88)
Q3: (7234, <13,019)	930	53	1.33 (0.84, 2.10)	142	1.06 (0.63, 1.78)	466	1.03 (0.65, 1.65)
Q4: ≥13,019	929	66	1.65 (1.05, 2.58)	170	1.25 (0.75, 2.07)	539	1.27 (0.80, 2.01)
P-trend			0.039		0.366		0.418

[1]BaP, benzo[α]pyrene; DiMeIQX, 2-amino-3,4,8-trimethylimidazo[4,5-f]-quinoxaline; max, maximum; MeIQX, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; min, minimum; NSAID, nonsteroidal anti-inflammatory drug; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; Q, quartile; ref, reference; SSL, sessile serrated lesion.

[2]ORs and 95% CIs were derived from multinomial logistic regression models adjusted for age, sex, race, study site, educational attainment, indication for colonoscopy, alcohol intake, smoking history, physical activity, BMI, total energy intake, and NSAID use. Statistical significance was set at $P < 0.0167$.

increased risk of SSL, the risks of SSLs were suggestively or significantly increased in comparison to HPs and ADs. Inferred MeIQX was associated with a strong increased risk of SSLs in comparison to controls, HPs, or ADs. The association was null for the other inferred meat mutagens investigated.

SSLs are a type of serrated polyp (SP) along with HPs and traditional serrated adenomas. Due to the lack of a consensus definition until 2010, many historical studies that have evaluated SP risk have not been able to differentiate SSLs from HPs and may also have misclassification of SP subtype (8). Thus, although there are a few studies, including our own (16), which have evaluated meat intake (20–24), well-done meat intake (17, 25, 26), and inferred meat-mutagen intake (25, 27) with risks of SPs or HPs, there is no other study that has evaluated all of these factors in relation to SSL risk. A recent study evaluated red meat intake with risk of nonadvanced and advanced adenomas, which included some SSLs (20). They confirmed our previous finding of an association between red meat intake and polyp risk. In a recent meta-analysis of risk factors for SPs, there was no observed association between processed meat intake and SP risk (28); however, they were unable to evaluate SSL risk. Future analyses need to make the distinction between HPs and SSLs as risk factors may differ between these polyp types.

Unlike previous studies that found a strong association between inferred meat-mutagen exposure and AD or SP risk (29), with the exception of MeIQX, the associations with SSL risk in this study were null across all other inferred meat mutagens. MeIQX is the mutagen most closely derived from red meat (30). The mutagenicity of MeIQX has been demonstrated in animal studies (29). One potential mechanism that could explain this is the formation of DNA adducts (15), which increase with the intake of dietary HCAs and PAHs.

In this study, the overall intakes of red and processed meats were slightly more strongly associated with SSL risk than well-done intakes of these meats, suggesting that it may not be well-doneness per se that is responsible for the increased risk. This observation could be the result of a limited sample size of individuals who consume well-done meats, or it could be

because of other mechanisms unrelated to PAHs and HCAs. Meat also contains N-nitroso compounds and heme iron (15). The mechanism for each of these components is different so it is critical to evaluate the evidence for each component separately in future studies. Other possible mechanisms of meat carcinogenicity include effects of bile acids on inflammation or cancer stem cells (31, 32).

Larger studies of SSLs could help confirm or counter the null findings in this study. Specifically, this study might have been underpowered to observe weak associations between the other HCAs and PAHs. However, the observed and strong statistically significant associations despite a limited sample size of SSLs relative to the other polyp types suggest that SSL risk is significantly increased by red meat intake and MeIQX exposure may be one of the mechanisms for this association. Additional studies are needed to evaluate other possible mechanisms.

Recall bias is always a concern in a case-control study; however, most study participants completed the telephone questionnaire within 13 d of their colonoscopy, including before they may have received their final report, and polyps are, in general, considered a benign diagnosis. In addition, most participants with an SSL would have been told that they have an HP as there was not a standardized diagnosis of this polyp type during the period of the study. We cannot preclude the possibility that some SSLs were missed during the colonoscopy, resulting in misclassification of the case status. However, SSLs are a rare polyp and missed SSLs are very rare; therefore, the potential case misclassification is unlikely to explain the observed associations. We did not include intakes of all meat types (e.g., lamb, goat, and turkey) and so may have underestimated intakes of red meat and poultry for some participants. There could have been errors in the HCA-exposure measurement; however, any misclassification is likely to be nondifferential, which tends to bias results towards the null. Our study is strengthened by the standardized pathological review of all polyps removed from study participants, the extensive information collected on meat intake and cooking preferences, and a population with a wide range of characteristics and behaviors.

Meat intake and well-done meat intake are factors that can be modified in the diet; therefore, particularly for SSLs as well as other polyp types, strategies such as reducing red and processed-meat intakes may be important for preventing CRC. Future studies are needed to confirm or refute the findings in this study. In addition, a better understanding of all of the mechanisms by which meat intake may affect SSL risk, such as heme and N-nitroso compounds, is needed. Finally, future studies should also evaluate interindividual differences in metabolism, such as HCA-metabolizing enzymes and heme or N-nitroso–metabolizing enzymes, which may affect susceptibility at equivalent exposure levels.

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